

INTERNATIONAL SEARCH REPORT

International Application No
PCT/GB2004/002938

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07F15/00 C07D207/14

According to International Patent Classification (IPC) or to both national classification and IPC

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
IPC 7 C07F C07D

Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched

Electronic data base consulted during the international search (name of data base and, where practical, search terms used)

EPO-Internal, WPI Data, PAJ, CHEM ABS Data

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 03/048173 A (MALAN CHRISTOPHE GUILLAUME ; CHIROTECH TECHNOLOGY LTD (GB); HENSCHKE J) 12 June 2003 (2003-06-12) the whole document	1-22
A	EP 1 134 226 A (TAKASAGO PERFUMERY CO LTD) 19 September 2001 (2001-09-19) the whole document	1-22
A	US 2002/095056 A1 (COBLEY CHRISTOPHER JAMES ET AL) 18 July 2002 (2002-07-18) the whole document	1-22
	-/--	

☒ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in annex.

* Special categories of cited documents:

- *A* document defining the general state of the art which is not considered to be of particular relevance
- *E* earlier document but published on or after the international filing date
- *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified)
- *O* document referring to an oral disclosure, use, exhibition or other means
- *P* document published prior to the international filing date but later than the priority date claimed

- *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention
- *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
- *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art.
- * & * document member of the same patent family

Date of the actual completion of the international search

1 December 2004

Date of mailing of the international search report

21/12/2004

Name and mailing address of the ISA
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C.(Continuation) DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	<p>NAGAMANI ET AL.: "Pyrrolidyl Polyamines: Branched, Chiral Polyamine Analogues That Stabilize DNA Duplexes and Triplexes"</p> <p>ORGANIC LETTERS, vol. 3, no. 1, 2001, pages 103-106, XP002305948 Cpds. 4, 9</p> <p>-----</p>	1-22

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Box II Observations where certain claims were found unsearchable (Continuation of Item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☐ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:
2. ☒ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
see FURTHER INFORMATION sheet PCT/ISA/210
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of Item 3 of first sheet)

This International Searching Authority found multiple inventions in this International application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
☐ No protest accompanied the payment of additional search fees.

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FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box II.2

Claims Nos.: -

Present claims 1-22 relate to an extremely large number of possible compounds and uses thereof.

Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds / uses claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely

a chiral catalyst

comprising a ruthenium complex in which the central metal is coordinated by a chiral bis(phosphine) and a chiral diamine of formula (I)

Furthermore the initial phase of the search revealed a large number of documents relevant to the assessment of novelty of the diamines (III) as defined in claims 23-25. So many documents were retrieved that it is impossible to determine which parts of the claims may be said to define subject-matter for which protection might legitimately be sought (Article 6 PCT). The last document cited in this Report discloses the compound as defined claim 25 and thus takes away the novelty of claims 23-25. Apart from this document there are other prior art disclosures comprising subject-matter which is detrimental for the novelty of claims 23 and 24.

For these reasons claims 23-25 have not been searched.

The applicant's attention is drawn to the fact that claims relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure. If the application proceeds into the regional phase before the EPO, the applicant is reminded that a search may be carried out during examination before the EPO (see EPO Guideline C-VI, 8.5), should the problems which led to the Article 17(2) declaration be overcome.

INTERNATIONAL SEARCH REPORT

Information on patent family members

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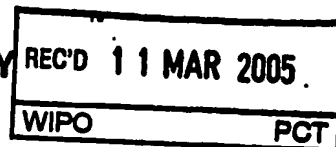
Patent document cited in search report		Publication date		Patent family member(s)		Publication date
WO 03048173	A	12-06-2003	EP	1458731 A1		22-09-2004
			WO	03048173 A1		12-06-2003
EP 1134226	A	19-09-2001	JP	2001261689 A		26-09-2001
			EP	1134226 A2		19-09-2001
			US	2001039354 A1		08-11-2001
US 2002095056	A1	18-07-2002	AU	7089201 A		05-02-2002
			CA	2415738 A1		31-01-2002
			EP	1305278 A1		02-05-2003
			WO	0208169 A1		31-01-2002
			JP	2004504371 T		12-02-2004
			AT	263176 T		15-04-2004
			AU	6251001 A		17-12-2001
			CA	2410410 A1		13-12-2001
			DE	60102587 D1		06-05-2004
			EP	1299401 A1		09-04-2003
			WO	0194359 A1		13-12-2001
			JP	2003535869 T		02-12-2003
			US	2002035285 A1		21-03-2002



PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY (Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)



Applicant's or agent's file reference SYN 60018WO	FOR FURTHER ACTION		See Form PCT/PEA416
International application No. PCT/GB2004/002938	International filing date (day/month/year) 07.07.2004	Priority date (day/month/year) 15.07.2003	
International Patent Classification (IPC) or national classification and IPC C07F15/00, C07D207/14			
Applicant JOHNSON MATTHEY PLC et al.			
<p>1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.</p> <p>2. This REPORT consists of a total of 5 sheets, including this cover sheet.</p> <p>3. This report is also accompanied by ANNEXES, comprising:</p> <p>a. <input checked="" type="checkbox"/> sent to the applicant and to the International Bureau a total of 3 sheets, as follows:</p> <p style="margin-left: 20px;"><input checked="" type="checkbox"/> sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).</p> <p style="margin-left: 20px;"><input type="checkbox"/> sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.</p> <p>b. <input type="checkbox"/> (sent to the International Bureau only) a total of (Indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).</p>			
<p>4. This report contains indications relating to the following items:</p> <p><input checked="" type="checkbox"/> Box No. I Basis of the opinion</p> <p><input type="checkbox"/> Box No. II Priority</p> <p><input type="checkbox"/> Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability</p> <p><input type="checkbox"/> Box No. IV Lack of unity of invention</p> <p><input checked="" type="checkbox"/> Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement</p> <p><input type="checkbox"/> Box No. VI Certain documents cited</p> <p><input type="checkbox"/> Box No. VII Certain defects in the international application</p> <p><input type="checkbox"/> Box No. VIII Certain observations on the international application</p>			
Date of submission of the demand 24.01.2005		Date of completion of this report 10.03.2005	
Name and mailing address of the international preliminary examining authority:  European Patent Office D-80298 Munich Tel. +49 89 2399 - 0 Tx: 523656 epmu d Fax: +49 89 2399 - 4465		Authorized Officer Fritz, M Telephone No. +49 89 2399-2792 	

**INTERNATIONAL PRELIMINARY REPORT
ON PATENTABILITY**

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Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.
- ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
- ☐ international search (under Rules 12.3 and 23.1(b))
 - ☐ publication of the international application (under Rule 12.4)
 - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)
2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

Description, Pages

1-24 as originally filed

Claims, Numbers

1-20 received on 24.01.2005 with letter of 20.01.2005

- ☐ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing
3. ☐ The amendments have resulted in the cancellation of:
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:
4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
- ☐ the description, pages
 - ☐ the claims, Nos.
 - ☐ the drawings, sheets/figs
 - ☐ the sequence listing *(specify)*:
 - ☐ any table(s) related to sequence listing *(specify)*:

* If item 4 applies, some or all of these sheets may be marked "superseded."

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Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes: Claims	1-20
	No: Claims	
Inventive step (IS)	Yes: Claims	1-20
	No: Claims	
Industrial applicability (IA)	Yes: Claims	1-20
	No: Claims	

2. Citations and explanations (Rule 70.7):

see separate sheet

Re Item V

Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

- D1: WO 03/048173 A (MALAN CHRISTOPHE GUILLAUME ; CHIROTECH TECHNOLOGY LTD (GB); HENSCHKE J) 12 June 2003 (2003-06-12)
D2: EP-A-1 134 226 (TAKASAGO PERFUMERY CO LTD) 19 September 2001 (2001-09-19)
D3: US 2002/095056 A1 (COBLEY CHRISTOPHER JAMES ET AL) 18 July 2002 (2002-07-18)

The present application relates to chiral catalysts (claims 1-18), the use thereof for the asymmetric hydrogenation of ketones and imines (claims 19-20).

In the chiral diamine ligands of the complexes as claimed in the present case the two amino groups are separated by 3 or 4 optionally substituted C-atoms thereby forming a 6- or 7-membered ring together with the central metal, whereas the chiral diamines employed in comparable prior art documents such as D1-D3 always form 5-membered rings with the central ruthenium atom, i.e. their geometry is more rigid as that of the complexes according to the present case.

The novelty of claims 1-20 is therefore acknowledged (Article 33(2) PCT).

Closest prior art is D1.

The problem of the present application was to provide further ruthenium complexes comprising a chiral bis(phosphine) and a chiral diamine as ligands to be employed as catalysts for asymmetric hydrogenation.

This problem has been solved, as can be seen in the description. :

As the use of a chiral diamine forming a larger ring with the central ruthenium is nowhere suggested in D1, the resulting compounds as described in the present case are representatives of a novel class of catalysts and as such not obvious for the man skilled in

**INTERNATIONAL PRELIMINARY
REPORT ON PATENTABILITY
(SEPARATE SHEET)**

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the art.

An inventive step in the sense of Article 33(3) PCT can therefore be acknowledged for the subject-matter of claims 1-20.

Further objections (which could be dealt with in the National Phase):

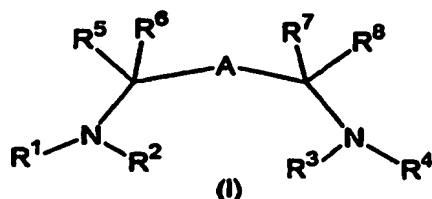
Contrary to the requirements of Rule 5.1(a)(ii) PCT, the relevant background art disclosed in the document D1 is not mentioned in the description, nor is this document identified therein.

The requirements of Article 6 PCT are not fulfilled for claim 1, as the additional meanings of R⁵, R⁶, R⁷ and R⁸ given in claims 7 and 8 have not been inserted in the definition of these groups in claim 1.

The description has not been brought in conformity with the amended claims.

Claims.

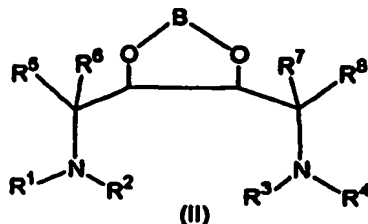
1. A chiral catalyst comprising the reaction product of a ruthenium compound, a chiral bis(phosphine) and a chiral diamine of formula (I)



In which R^1 , R^2 , R^3 or R^4 are independently hydrogen, a saturated or unsaturated alkyl, or cycloalkyl group, an aryl group, a urethane or sulphonyl group and R^5 , R^6 , R^7 or R^8 are independently hydrogen, a saturated or unsaturated alkyl or cycloalkyl group, or an aryl group, at least one of R^1 , R^2 , R^3 or R^4 is hydrogen and A is a linking group comprising one or two substituted or unsubstituted carbon atoms.

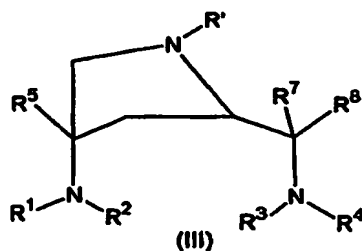
2. A catalyst according to claim 1 wherein the chiral bis(phosphine) is P-Phos, tol-P-Phos or xyl-P-Phos.
3. A catalyst according to claim 1 or claim 2 wherein R^1 , R^2 , R^3 and R^4 are the same or different and are selected from hydrogen, methyl, ethyl, isopropyl, cyclohexyl, phenyl or 4-methylphenyl groups.
4. A catalyst according to claim 1 or claim 2 wherein R^1 and R^2 are linked or R^3 and R^4 are linked so as to form a 4 to 7-membered ring structure incorporating the nitrogen atom.
5. A catalyst according to any one of claims 1 to 4 wherein R^5 , R^6 , R^7 and R^8 are the same or different and are selected from hydrogen, methyl, ethyl, propyl, iso-propyl, butyl, iso-butyl, sec-butyl, tert-butyl, cyclohexyl or substituted or unsubstituted phenyl or naphthyl groups.
6. A catalyst according to any one of claims 1 to 4 wherein one or more of R^5 , R^6 , R^7 or R^8 form one or more ring structures with the linking group A.
7. A catalyst according to any one of claims 1 to 6 wherein a substituting group on the carbon atom of linking group A is alkyl (C1-C20), alkoxy (C1-C20) or amino or forms one or more ring structures incorporating one or more carbon atoms making up the linking group.

8. A catalyst according to claim 1 or claim 2 wherein the chiral diamine is of formula (II)



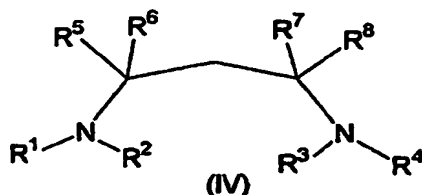
wherein B is a linking group comprising one or two substituted or unsubstituted carbon atoms.

9. A catalyst according to claim 8 wherein R^1 , R^2 , R^3 , R^4 are hydrogen, R^5 , R^6 , R^7 and R^8 are hydrogen or alkyl groups and B comprises $C(CH_3)_2$ or $(CH_3)(OCH_3)C-C(CH_3)(OCH_3)$.
10. A catalyst according to claim 8 or claim 9 wherein the chiral diamine is selected from 3-Aminomethyl-5,6-dimethoxy-5,6-Dimethyl[1,4]-dioxan-2-yl]-methylamine (DioBD) or 2,3-O-Isopropylidenebutane 1,4 diamine (DAMTAR).
11. A catalyst according to claim 1 or claim 2 wherein the chiral diamine is of formula (III)

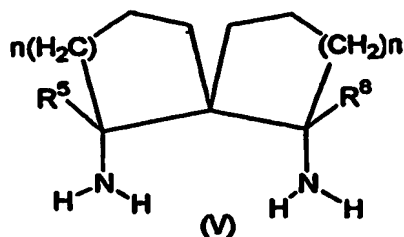


wherein R' is a protecting group.

12. A catalyst according to claim 11 wherein R^1 , R^2 and R^5 are hydrogen, R^3 and R^4 are hydrogen or alkyl, R^7 and R^8 are hydrogen, alkyl or aryl and R' is selected from an alkyl, aryl, carboxylate, amido or sulphonate protecting group.
13. A catalyst according to claim 11 or claim 12 wherein the chiral diamine is 4-Amino-2-aminomethylpyrrolidine-1-carboxylic acid *tert*-butyl ester (PyrBD).
14. A catalyst according to claim 1 or claim 2 wherein the chiral diamine is of formula (IV)



15. A catalyst according to claim 14 wherein $R^1, R^2, R^3, R^4, R^6, R^7$ are hydrogen and R^5 and R^8 are aryl or substituted aryl groups.
16. A catalyst according to claim 14 or claim 15 wherein the chiral diamine is Diphenyl-1,3-propanediamine (Dppn).
17. A catalyst according to claim 1 or claim 2 wherein the chiral diamine is of formula (V).



wherein $n = 1$ or 2 .

18. A catalyst according to claim 17 wherein R^5 and R^8 are hydrogen.
19. The use of catalysts of claims 1 to 18 for the asymmetric hydrogenation of ketones and imines.
20. The use of catalysts according to claim 19 for the hydrogenation of alkyl ketones of formula $RCOR'$ in which R and R' are substituted or unsubstituted, saturated or unsaturated C1-C20 alkyl or cycloalkyl which may be linked and form part of a ring structure.